

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Michael Boyd, <i>et al.</i>		
Serial No.:	10/581,692	Case No. MC098YP	Art Unit: 1626
Filed:	June 6, 2006		
For:	CATHEPSIN CYSTEINE PROTEASE INHIBITORS		

Examiner: J. Kosack

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF CAMERON BLACK, PhD

Sir:

I Cameron Black, PhD.,

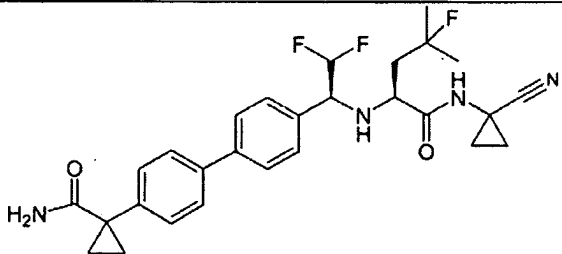
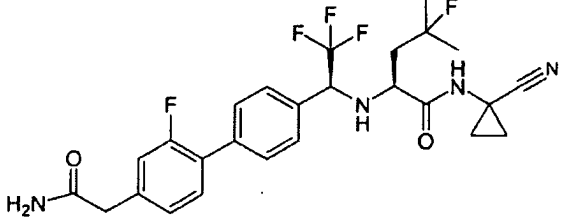
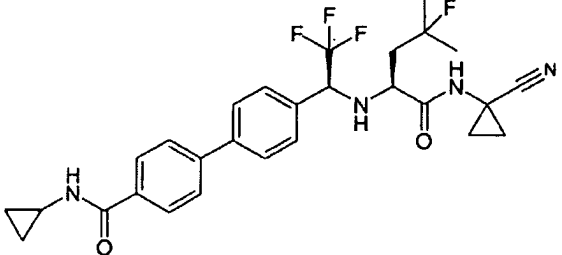
do hereby declare that

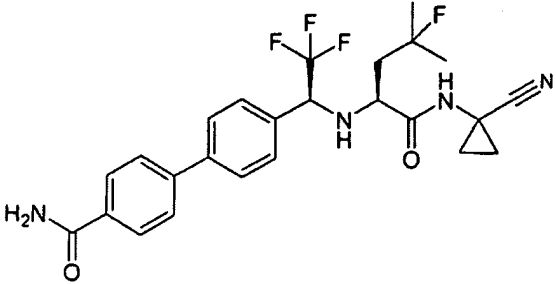
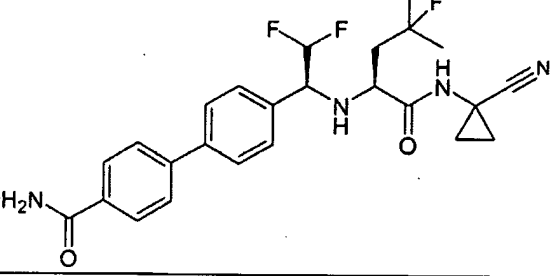
1. I am employed by Merck Frosst Canada Ltd., Inc as the Director of Medicinal Chemistry. My *curriculum vitae* is attached as Exhibit 1.
2. My responsibilities at Merck Frosst Canada Ltd. include basic research. I worked extensively on the discovery of cathepsin K inhibitors. During the course of that work, my team and I discovered many cathepsin K inhibitors, including those claimed in the instant application.
3. The compounds of the instant invention are amide-substituted peptide nitriles that are useful as selective inhibitors of cathepsin K. The alkyl spacing between the biaryl group and the amide moiety unexpectedly results in a favorable profile when compared to analogues wherein the biaryl group is directly bonded to the amide moiety. The compounds of the instant invention (e.g, Compounds 1-2)

have improved selectivity over cathepsins S when compared to representative compounds in Bayly et al. (Compounds 3-5). The selectivity is assessed by comparing the IC_{50} vs cathepsin S to the IC_{50} vs cathepsin K. Achieving high levels of selectivity over cathepsin S inhibition was a primary objective of our research and is important due to the known effects on the immune system found in mice with a cathepsin S gene deletion (Driessen et al, *J Cell Biol.*, **147**, 775, 1999; Nakagawa et al, *Immunity*, **10**, 207, 1999).

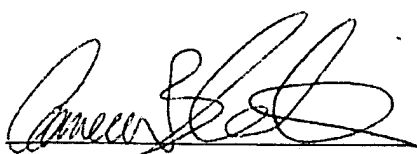
Table 1 summarizes the data described above:

TABLE 1

Number	Structure	Humanized rabbit Cathepsin K	Human Cathepsin S	Selectivity Ratio S/K
1		0.67 nM	829 nM	1240
2		0.21 nM	274 nM	1300
3		2.5 nM	300 nM	120

4		0.54 nM	50 nM	93
5		1.3 nM	177 nM	136

4. These results were unexpected, and said results were realized prior to the filing date of the above-captioned application.
5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 or Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.


Cameron Black, PhD

June 23, 2009
Date

W. CAMERON BLACK

CONTACT INFORMATION:

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EDUCATION:

- | | |
|------|--|
| 1992 | Ph.D. in Chemistry
Harvard University, Cambridge MA |
| 1987 | B.Sc. in Chemistry, High Honours
University of Saskatchewan, Saskatoon SK |

PROFESSIONAL EXPERIENCE:

- | | |
|-----------|--|
| 2005- | Director, Medicinal Chemistry , Merck Frosst Canada Ltd <ul style="list-style-type: none">- Responsible for Lead Optimization projects in the area of Metabolic Disorders resulting in two development compounds- Responsible for Lead Identification group- Responsible for Technology-Enabled Synthesis group- Chair of MRL Flow Chemistry User's Group |
| 2002-2005 | Senior Research Fellow , Merck Frosst Canada Ltd <ul style="list-style-type: none">- Synthesis of selective cathepsin K inhibitors<ul style="list-style-type: none">- Discovered key pharmacophore for Cat K inhibitors- Led chemistry team to identify odanacatib- Chaired Product Development Team for odanacatib, guiding its development into Phase IIb |
| 1996-2001 | Research Fellow , Merck Frosst Canada Ltd <ul style="list-style-type: none">- Synthesis of selective cyclooxygenase-2 inhibitors<ul style="list-style-type: none">- Led chemistry team to identify firocoxib (Previcox)- Synthesis of caspase-3 inhibitors<ul style="list-style-type: none">- Organized and led MRL Brain Penetration Task Force |

- 1992-1996 **Senior Research Chemist, Merck Frosst Canada Ltd**
 - Synthesis of selective cyclooxygenase-2 inhibitors
 - Contributed to identification of etoricoxib (Arcoxia)
- 1988-1992 **Graduate Research with Professor David A. Evans,**
 Harvard University
 - Total Synthesis of A83543A (Lepicidin)

PROFESSIONAL TRAINING:

- | | |
|--------------|--------------------------------|
| Jan-Dec 2008 | Leadership Development Program |
| Mar 2006 | Business Leadership Program |
| Jan 2000 | Management Grid |

ACADEMIC AND PROFESSIONAL HONORS:

- Merck Special Achievement Award, 2008
 Merck Leader Award, 2005
 Merck Key R&D Award, 1997, 1999, 2004, 2005
 Eli Lilly Predoctoral Fellow, 1991
 NSERC Undergraduate Research Award, 1987
 Chemical Institute of Canada Prize, 1986

PUBLICATIONS:

1. David A. Evans, W. Cameron Black. "Synthesis of (+)-A83543A Aglycon" *J. Am. Chem. Soc.* 114 (1992): 2260-2262.
2. C. Black, P. Lario, A.P. Masters, T.S. Sorensen, F. Sun. "A new synthesis of in situ cyclopropanones and the observation of thermal cyclopropanedienol rearrangement" *Can. J. Chem.* 71 (1993): 1910-1918.
3. David A. Evans, W. Cameron Black. "Total Synthesis of (+)-A83543A [(+)-Lepicidin A]" *J. Am. Chem. Soc.* 115 (1993): 4497-4513.
4. P. Prasit, W. C. Black, C.-C. Chan, A.W. Ford-Hutchinson, J.Y. Gauthier, R. Gordon, D. Guay, S. Kargman, C.K. Lau, C.-S. Li, J. Mancini, N. Ouimet, P. Roy, P. Tagari, P. Vickers, E. Wong, R.N. Young, R. Zamboni "L-745,337: a selective cyclooxygenase-2 inhibitor." *Med. Chem. Res.* 5 (1995): 364-74.
5. C.S. Li, W. Cameron Black, Chi-Chung Chan, Anthony W. Ford-Hutchinson, Jacques Yves Gauthier, Robert Gordon, Daniel Guay, Stacia Kargman, Cheuk K. Lau, Joe Mancini, Nathalie Ouimet, Patrick Roy, Philip Vickers, Elizabeth Wong, Robert N. Young, Robert Zamboni, Petpiboon Prasit "Cyclooxygenase-2 inhibitors. Synthesis and pharmacological

activities of 5-methanesulfonamido-1-indanone derivatives." *J. Med. Chem.* 38 (1995): 4897-4905.

6. W. C. Black, C. Bayly, M. Belley, C.-C. Chan, S. Charleson, D. Denis, J. Y. Gauthier, R. Gordon, D. Guay, S. Kargman, C. K. Lau, Y. Leblanc, J. Mancini, M. Ouellet, D. Percival, P. Roy, K. Skorey, P. Tagari, P. Vickers, E. Wong, L. Xu, P. Prasit. "From indomethacin to a selective COX-2 inhibitor: development of indolalkanoic acids as potent and selective cyclooxygenase-2 inhibitors." *Bioorg. Med. Chem. Lett.* 6 (1996): 725-30
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8. W. Cameron Black, Andre Giroux, Grace Greidanus. "Silyloxy-cope rearrangement of chiral aldol adducts." *Tetrahedron Lett.* 37 (1996): 4471-74.
9. Jacques Yves Gauthier, Yves Leblanc, W. Cameron Black, Chi-Chung Chan, Wanda A. Cromlish, Robert Gordon, Brian P. Kennedy, Cheuk K. Lau, Serger Leger, Zhaoyin Wang, Diane Ethier, Jocelyn Guay, Joseph Mancini, Denis Riendeau, Philip Tagari, Philip Vickers, Elizabeth Wong, Lijing Xu, Peptiboon Prasit. "Synthesis and biological evaluation of 2,3-diarylthiophenes as selective COX-2 inhibitors. Part II: replacing the heterocycle." *Bioorg. Med. Chem. Lett.* 6 (1996): 87-92.
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11. W. Cameron Black, Benoit Guay, Frank Scheuermeyer. "Metalation of nitroaromatics with *in situ* electrophiles." *J. Org. Chem.* 62 (1997): 758-60.
12. W. Cameron Black, Benoit Guay. "Synthesis of sulfonyl flosulide." *Synthesis* (1998): 1101-3.
13. C. I. Bayly, W. C. Black, S. Leger, N. Ouimet, M. Ouellet, M. D. Percival. "Structure-based design of COX-2 selectivity into flurbiprofen." *Bioorg. Med. Chem. Lett.* 9 (1999): 307-12.
14. W. Cameron Black, Christine Brideau, Chi-Chung Chan, Stella Charleson, Nathalie Chaurct, David Clavcau, Diane Éthier, Robert Gordon, Gillian Greig, Jocelyne Guay, Gregory Hughes, Paule Jolicoeur, Yves Leblanc, Deborah Nicoll-Griffith, Nathalie Ouimet, Denis Riendeau, Denise Visco, Zhaoyin Wang, Lijing Xu, Peptiboon Prasit. "2,3-Diarylcyclopentenones as orally active, highly selective selective cyclooxygenase-2 inhibitors." *J. Med. Chem.* 42 (1999): 1274-81.

15. Chun-Sing Li, W. Cameron Black, Christine Brideau, Chi Chung Chan, Stella Charleson, Wanda A. Cromlish, David Claveau, Jacques Yves Gauthier, Robert Gordon, Gillian Greig, Erich Grimm, Jocelyne Guay, Cheuk K. Lau, Denis Riendeau, Michel Thérien, Denise M. Visco, Elizabeth Wong, Lijing Xu, Petpiboon Prasit. "A new structural variation on the methanesulfonylphenyl class of selective cyclooxygenase-2 inhibitors" *Bioorg. Med. Chem. Lett.* 9 (1999): 3181-86.
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19. W. Cameron Black, Christine Brideau, Chi-Chung Chan, Stella Charleson, Wanda Cromlish, Robert Gordon, Erich L. Grimm, Gregory Hughes, Serge Leger, Chun-Sing Li, Denis Riendeau, Michel Therien, Zhaoyin Wang, Li-Jing Xu, Petpiboon Prasit. "3,4-Diaryl-5-hydroxyfuranones: Highly Selective Inhibitors of Cyclooxygenase-2 with Aqueous Solubility." *Bioorg. Med. Chem. Lett.* 13 (2003): 1195-98.
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22. Jean-Pierre Falgueyret, W. Cameron Black, Wanda Cromlish, Sylvie Desmarais, Sonia Lamontagne, Christophe Mellon, Denis Riendeau, Sevgi Rodan, Paul Tawa, Gregg Wesolowski, Kathryn E. Bass, Shankar Venkatraman, M. David Percival. "An activity-based probe for the determination of cysteine cathepsin protease activities in whole cells." *Anal. Biochem.* 335 (2004): 218-227.
23. W. Cameron Black. "Selective Cyclooxygenase-2 Inhibitors" *Ann. Reports Med.Chem.* 39 (2004): 125-138.
24. W. Cameron Black, Christopher I. Bayly, Dana E. Davis, Sylvie Desmarais, Jean-Pierre Falgueyret, Serge Léger, Chun Sing Li, Frédéric Massé, Daniel J. McKay, James T.

- Palmer, M. David Percival, Joël Robichaud, Nancy Tsou, Robert Zamboni. "Trifluoroethylamines as amide isosteres in inhibitors of cathepsin K." *Bioorg. Med. Chem. Lett.* 15 (2005): 4741-44.
25. Jean-Pierre Falgueyret, Sylvie Desmarais, Renata Oballa, W. Cameron Black, Wanda Cromlish, Karine Khougaz, Sonia Lamontagne, Frederic Massé, Denis Riendeau, Sylvie Toulmond, M. David Percival. "Lysosomotropism of basic cathepsin K inhibitors contributes to increased cellular potencies against off-target cathepsins and reduced functional selectivity." *J. Med. Chem.* 48 (2005): 7535-43.
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 30. W. Cameron Black, M. David Percival. "The consequences of lysosomotropism on the design of selective cathepsin K inhibitors." *ChemBiochem.* 7 (2006): 1525-35.
 31. W. Cameron Black, M. David Percival. "Cathepsin K Inhibitors" *Ann. Reports Med.Chem.* 42 (2007): 111-127.
 32. Joël Robichaud, Christopher I. Bayly, W. Cameron Black, Sylvie Desmarais, Serge Léger, Frédéric Massé, Daniel J. McKay, Renata M. Oballa, Julie Paquet, M. David Percival, Jean-François Truchon, Gregg Wesolowski and Sheldon N. Crane. "B-Substituted cyclohexanecarboxamide cathepsin K inhibitors: Modification of the 1,2-disubstituted aromatic core." *Bioorg. Med. Chem. Lett.* 17 (2007): 3146-51.
 33. Serge Léger, Christopher I. Bayly, W. Cameron Black, Sylvie Desmarais, Jean-Pierre Falgueyret, Frédéric Massé, M. David Percival and Jean-François Truchon. "Primary

- amides as selective inhibitors of cathepsin K" *Bioorg. Med. Chem. Lett.* 17 (2007): 4328-32.
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 35. Sylvie Desmarais, W. Cameron Black, Renata Oballa, Sonia Lamontagne, Denis Riendeau, Paul Tawa, Le Thi Duong, Maureen Pickarski, and M. David Percival. "Effect of Cathepsin K Inhibitor Basicity on in Vivo Off-Target Activities" *Mol Pharmacol* 73 (2008): 147-56.
 36. Jacques Yves Gauthier, Nathalie Chauret, Wanda Cromlish, Sylvie Desmarais, Le T. Duong, Jean-Pierre Falgout, Donald B. Kimmel, Sonia Lamontagne, Serge Léger, Tammy LeRiche, Chun Sing Li, Frédéric Massé, Daniel J. McKay, Deborah A. Nicoll-Griffith, Renata M. Oballa, James T. Palmer, M. David Percival, Denis Riendeau, Joel Robichaud, Gideon A. Rodan, Sevgi B. Rodan, Carmei Seto, Michel Thérien, Vouy-Linh Truong, Michael C. Venuti, Gregg Wesolowski, Robert N. Young, Robert Zamboni, and W. Cameron Black. "The discovery of odanacatib (MK-0822), a selective inhibitor of cathepsin K" *Bioorg. Med. Chem. Lett.* 18 (2008): 923-8.
 37. Joël Robichaud, W. Cameron Black, Michel Thérien, Julie Paquet, Renata M. Oballa, Christopher I. Bayly, Daniel J. McKay, Qingping Wang, Elise Isabel, Serge Léger, Christophe Mellon, Donald B. Kimmel, Gregg Wesolowski, M. David Percival, Frédéric Massé, Sylvie Desmarais, Jean-Pierre Falgout, Sheldon N. Crane. "Identification of a Nonbasic, Nitrile-Containing Cathepsin K Inhibitor (MK-1256) that is Efficacious in a Monkey Model of Osteoporosis" *J. Med. Chem.* 51 (2008): 6410-20.
 38. Michael J. Boy, Sheldon N. Crane, Joël Robichaud, John Scheigetz, W. Cameron Black, Nathalie Chauret, Qing-ping Wang, Frédéric Massé, Renata M. Oballa, *Bioorg. Med. Chem. Lett.* 19 (2009): 675-9.

PRESENTATIONS:

1. *Asymmetric induction using aldol/oxy-cope methodology.*
 - University of Saskatchewan, Saskatoon, March 29, 1994
2. *Asymmetric induction using aldol/oxy-cope methodology.*
 - 4th ICCSA Meeting, Nashville, Indiana, Sept. 13, 1994.
3. *From Indomethacin to a Cox-2 Selective Inhibitor.*
 - Inflammation '95, Brighton, England, Sept. 21, 1995.
 - University of Saskatchewan, Saskatoon, Nov. 28, 1995.
 - University of Manitoba, Winnipeg, Nov. 29, 1995.
 - Ottawa-Carleton Chemistry Symposium, Ottawa, May 7, 1996.
 - Atlantic Student Chemistry Conference, Antigonish, May 16, 1996.

4. *Nicotinyl Aspartyl Ketones are Selective Inhibitors of Caspase-3.*
 - 4th International Symposium on Medicinal Chemistry of Neurodegenerative Diseases, Cancun, Mexico, Jan. 31, 2000
5. *The Search for Inhibitors of the Cysteine Protease Caspase-3.*
 - University of Alberta, Edmonton, Jan. 22, 2001.
 - University of Calgary, Calgary, Jan 23, 2001.
 - University of Saskatchewan, Saskatoon, Jan 25, 2001.
6. *The Discovery of ML-1,785,713, a COX-2 Selective Inhibitor for Animal Health*
 - 17th ISMC Meeting, Barcelona, Spain, Sept 1-5, 2002.
7. *The Design of Potent and Selective, Non-peptidic Nitrile Inhibitors of Cathepsin K*
 - Medicinal Chemistry Gordon Conference, New London NH, Aug. 1-6, 2004.
8. *Inhibitors of Cathepsin K: the Search for Better Treatments of Osteoporosis*
 - 15th QOMBOC, Gatineau, Quebec, Nov. 5-7, 2004.
9. *Use of enzyme probes to define cellular selectivity: application to the design of selective inhibitors of cathepsin K*
 - Pacificchem 2005, Honolulu, Hawaii, Dec 15-20, 2005
 - CSC, Halifax NS May 28-31, 2006
10. *The Discovery of MK-0822: A Selective Inhibitor of Cathepsin K for the Treatment of Osteoporosis*
 - ASMS, Åre, Sweden Mar 13, 2007
11. *Odanacatib (MK-822) is a potent and selective cathepsin K inhibitor that maintains its high selectivity in whole cell assays*
 - ASBMR, Honolulu, Hawaii, Sept. 16-19, 2007
12. *The Discovery of a Selective Cathepsin K Inhibitor*
 - IBMS, Davos, Switzerland, Mar 12, 2008
 - McMaster University, Hamilton ON, Aug 6, 2008
 - ASBMR, Montreal QC Sept 16, 2008
 - Carleton University, Ottawa ON, Nov 4, 2008
 - University of Toronto, Toronto ON, Dec 3, 2008

PATENTS:

1. *Alkylsulphonylamido-1-indanone derivatives as cyclooxygenase inhibitors.* U.S. Patent No. 5,409,944.
2. *1-Aroyl-3-indolyl alkanoid acids as antiinflammatory agents.* US Patent No. 5,436,265.
3. *N-Benzyl-3-indoleacetic acids as antiinflammatory drugs.* US Patent No. 5,510,368.
4. *N-benzylindol-3-yl propanoic acid derivatives as cyclooxygenase inhibitors.* US Patent 5,604,253.
5. *N-benzyl indol-3-yl butanoic acid derivatives as cyclooxygenase inhibitors.* US Patent 5,639,780.

6. *Diaryl-5-oxygenated-2-(5H)-furanones as Cox-2 inhibitors.* US Patent 5,691,374.
7. *3,4-Diaryl-2-hydroxy-2,5-dihydrofurans as prodrugs to Cox-2 inhibitors.* US Patent 5,698,584.
8. *Diphenyl Stilbenes as prodrugs to COX-2 inhibitors.* US Patent 5,733,909.
9. *Alkylated Styrenes as prodrugs to COX-2 inhibitors.* US Patent 5,789,413.
10. *Pyridinyl-2-cyclopenten-1-ones as selective cyclooxygenase-2 inhibitors.* US Patent 5,922,742.
11. *Alkylated Styrenes as prodrugs to COX-2 inhibitors.* US Patent 5,925,631.
12. *(Methylsulfonyl)phenyl-2-(5H)-furanones as COX-2 inhibitors.* U.S. Patent No. 5,981,576.
13. *Bisaryl COX-2 inhibiting compounds, compositions and methods of use.* U.S. Patent No. 5,994,379.
14. *(Methylsulfonyl)phenyl-2-(5H)-furanones as COX-2 Inhibitors.* U.S. Patent No. 6,020,343.
15. *3,4-Diaryl-2-hydroxy-2,5-dihydrofurans as prodrugs to Cox-2 inhibitors.* US Patent 6,057,319.
16. *(Methylsulfonyl)phenyl-2-(5H)-furanones as COX-2 Inhibitors.* U.S. Patent No. 6,169,188.
17. *Diphenyl-1,2,3-thiadiazole 3-oxides, compositions and methods of use.* U.S. Patent No. 6,211,210.
18. *Diaryl-2-(5H)-Furanones as COX-2 inhibitors.* U.S. Patent No. 6,222,048.
19. *Gamma.-keto acid dipeptides as inhibitors of caspase-3.* U.S. Patent No. 6,225,288.
20. *Gamma.-keto acid dipeptides as inhibitors of caspase-3.* U.S. Patent No. 6,525,025.
21. *Nicotinyl Aspartyl Ketones as Inhibitors of Caspase-3.* WO 200127085.
22. *Cathepsin Cysteine Protease Inhibitors.* U.S. Patent No. 7,012,075.
23. *Cyanoalkylamino derivatives as protease inhibitors.* U.S. Patent No. 7,371,747.
24. *Cathepsin Cysteine Protease Inhibitors.* U.S. Patent No. 7,375,134.
25. *4-Amino-azepan-3-one compounds as cathepsin K inhibitors useful in the treatment of osteoporosis.* WO 2004033445.
26. *Cathepsin Cysteine Protease Inhibitors.* U.S. Patent No. 7,405,229.
27. *Cathepsin Inhibitors.* WO 2005021487.
28. *Cathepsin Cysteine Protease Inhibitors.* WO 2005066159.
29. *Fluoroalkylamine Derivatives as Cathepsin Inhibitors.* WO2006128287.
30. *Cathepsin Cysteine Protease Inhibitors.* WO 2007003056.
31. *Heteroaromatic Compounds as Inhibitors of Stearoyl-Coenzyme A Delta-9 Desaturase.* WO 2007009236.
32. *Papain Family Cysteine Protease Inhibitors for the Treatment of Parasitic Diseases.* WO 2007012180.
33. *Composition for Inhibition of Cathepsin K.* WO 2007046842.